

REMARKS

Applicant addresses the Examiner's comments using the paragraph numbering of the office action. The amendment of the claims should not be construed as acquiescence in any ground of rejection.

3. Applicant disagrees with the Examiner's comments regarding priority. The '435 priority application describes the present methods as an "evolution of resequencing array designs" (a p. 2, lines 36-38). The '435 priority incorporates by reference WO95/11995 as describing resequencing arrays. WO95/11995 provides further explanation of such arrays including description of probes spanning a reference sequence. In the aggregate, these disclosures evidence applicant's possession of methods of iterative resequencing based on evolution of resequencing array designs including probes spanning a reference sequence.

Applicant notes that the issue of priority does not appear to be relevant to any of the cited references.

4-5. Claim 1 has been clarified to indicate that it is the probes that are immobilized on the at least one support.

6-7. Claims 1-3, and 5-15 stand rejected as anticipated by Gingeras. This rejection is respectfully traversed. Gingeras discusses iterative algorithms for analyzing the data from an array. However, these algorithms do not include designing a second array based on estimated sequence determined from a previous array, and then using the second array to obtain a reestimated sequence as claimed.

8-9. Claims 1-3, and 5-15 stand rejected as obvious over Erlich in view of Skiena. This rejection is respectfully traversed.

Ehrlich discusses uses probes complementary to variable regions of HLA genes to type which genes are present in an individual. Erlich does not teach probes

spanning a reference sequence. Erlich also does not teach designing a secondary array based on an estimated sequence, as acknowledged by the Examiner.

Skiena has been amply discussed in previous responses and the appeal brief. For the reasons provided therein, applicant maintains that Skiena does not disclose estimating or reestimating a target sequence, or designing a secondary array based on a reestimated target sequence.

Because of the deficiency in Erlich in disclosing probes spanning a target sequence and that of Skiena in disclosing estimating or reestimating a target sequence, it is respectfully submitted that the combination of references does not disclose all claim elements.

Further, the asserted motivation of "economy of synthesis, hybridization and costs" from Skiena would not have motivated the combination of this reference with Erlich. Erlich's method is relatively simple involving hybridizing a relatively small number of probes (up to about 14) to a target sequence, and determining whether each of them hybridizes. Although Ehrlich may mention the possibility of synthesizing sufficient target DNA to perform multiple hybridizations, he does not say that this is a problem. Moreover, Ehrlich teaches alternative methods in which the same target sample can be hybridized to multiple probes (col. 12, line 25-38). By contrast, Skiena's remarks regarding economy of his method were made in the context of comparing his own method with previous proposals to use very large arrays of complete sets of oligonucleotides (65k plus, see col. 3, line 53) for de novo sequencing by hybridization. Skiena's proposed solution is itself complex involving design of multiple arrays and algorithms to interpret them. Although Skiena's method might be economical compared with previous proposals for de novo sequencing, it would have appeared unnecessarily complex in the much simpler task of typing precharacterized HLA genes. Thus, Skiena's reference to economy would not have impelled the artisan to depart from Erlich's own teaching to attempt to incorporate the much more complex method of Skiena.

The dependent claims are all patentable for at least the same reasons as claim 1. However, applicant notes for the record disagreement with the Examiner's position that the elements of these claims are disclosed in the cited references.

10. Claim 4 stands rejected as obvious over Erlich in view of Skiena in further view of Dietrich. Claim 4 is distinguished for at least the same reasons as claim 1. In addition, it is respectfully submitted that the asserted motivation of a benefit of comparing human and primate target sequences would not have led one to modify the teaching of Erlich and Skiena to analyze a primate sequence based on a human reference sequence (or vice versa). To "establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the *specific* combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis supplied). Here, the alleged benefit of comparing human and primate sequences would arise regardless of how the sequences are determined, and provides no indication as to how the sequences should be determined. Thus, one reading Dietrich wanting to sequence additional primate or human sequences would not have been provided any reason to depart from the many conventional methods of determining sequences including dideoxy sequencing and Maxam Gilbert sequencing. As the Federal Circuit has cautioned, a "person of ordinary skill in the art is...*presumed to be one who thinks along the lines of conventional wisdom in the art...*," *Standard Oil Co. v American Cyanamid Co.*, 774 F.2d 448 (Fed. Cir. 1985), at p. 454 (emphasis added).

11-12. Claims 1-15 stand rejected under the obviousness-type double patenting doctrine over claims 42-47 of US 6,228,575. This rejection is respectfully traversed. The cited claims of the '575 patent have little in common with the presently claimed methods. The cited claims of the '575 patent are directed to methods of comparing hybridization patterns to associate a portion of the hybridization pattern with a species. The claims do not require *inter alia* estimating a sequence, reestimating a sequence, designing a second array based on an estimated sequence from the first array or hybridizing the same

target sequence to first and second arrays. The Examiner position that "comparing" and "assigning" mean the same as "estimating" and "reestimating" is incorrect. The "comparing" of the '575 patent refers to a comparison of hybridization patterns from first and second arrays and does not require sequence estimation. The "estimating" of the present claims is an estimate of sequence performed from the hybridization of the first array alone. It is this estimate that allows design of the second array. The "assigning" of a probability of the '575 patent refers to the assigning of a number representing a probability of a hybridization pattern being associated with a species. Such a probability is not an estimate, much less a reestimate of a nucleic acid sequence.

13. Claims 1-15 stand provisionally rejected for obviousness-type double patenting over claims 1-29 of copending application 10/229,319. This rejection is respectfully traversed. The claims of the '319 patent have little in common with the present claims. In the '319 patent, the first array of probes is used to identify polymorphic sites in different individuals, and the second array of probes is used to determine a polymorphic profile at these sites in a further individual. The method differs from that claimed *inter alia* in that the second array does not comprise probes complementary to and spanning the estimated sequence of the target nucleic acid determined from hybridization to the first array, the target nucleic acid applied to the second array is from a further individual, and the hybridization of the second array does not provide a reestimated sequence of the target nucleic acid hybridized to the first array.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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